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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
REDDIG, PETER J	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/854,811	REITER ET AL.	
	Examiner	Art Unit	
	Peter J. Reddig	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *53,58-64,67,70,71,74,77-88,91 and 93-100* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *53,58-64,67,70,71,74,77-88,91 and 93-100* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/11/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 11, 2007 has been entered.

2. An action on the RCE follows.

3. Claims 53, 58-64, 67, 70, 71, 74, 77-88, 91, 93-100 are currently pending and under consideration.

4. Rejections Maintained:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 53, 58-64, 67, 70, 71, 74, 77-88, 91, 93-97 remain rejected and new claims 98-100 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for the reasons previously set forth in the Office Action of July 7, 2006, section 5, pages 2-6 and the Office Action of June 22, 2004, section 8, pages 3-8.

Applicants argue that most of the concerns raised in the action relate to the induction of a cellular immune response. One concern raised by the Action is whether the length of the various peptide fragments set forth in the claims were too long to be active in inducing a cellular immune

response. In fact, professionally antigen presenting cells such as dendritic cells digest proteins into smaller peptides. In the lymph node, the DC will display these antigenic peptides on its surface by coupling them to MHC Class II molecules. This MHC:antigen complex is then recognized by T cells passing through the lymph node. Exogenous antigens are usually displayed on MHC Class II molecules, which interact with CD4+ helper T cells. CD4+ lymphocytes, or TH, are immune response mediators, and play an important role in establishing and maximizing the capabilities of the adaptive immune response. Thus, the length of a fragment is *no* bar to its suitability in generating such responses. A large fragment can be processed to provide a number of different subfragments to be presented on the surface of an Antigen Presenting Cell (see Exhibit A, pages 115 to 119 of Roitt et al., *Immunology,* 5th Edition, Mosby press, Philadelphia). Some such fragments will be of a length of sequence suitable for binding to an HLA allele. This comports with the results of Kiessling et al., already of record, who found the presence of $CD8^+$ reactive cells which recognized two of their peptide fragments in the serum of cancer patients *who had not been administered the PSCA peptide fragments.*

Applicants arguments have been carefully considered, but have not been found persuasive because Kiessling et al. does not teach the treatment of any cancer by inducing an immune response with any of the claimed proteins and the peptides taught by Kiessling et al. are not the peptides claimed and it cannot be determined if the claimed proteins will induce an immune response that is effective to treat any of the claimed cancers because it is not known and cannot be predicted if the claimed proteins will be processed and bind MHC molecules so as to be presented in a way that will elicit an immune response that is effective for immunotherapy of

cancer which is the clearly the contemplated use of the claimed method. Additionally, there is no teaching that any of the claimed peptides will interact with MHC Class II or class I molecules, which have specific constraints on are their ability to interact with a peptide, see the cited Roitt, thus it cannot be predicted that MHC class II or I will interact with the claimed proteins. Although Kiessling found $CD8^+$ reactive cells in prostate cancer patients that recognized two of their peptide fragments, the presence of these $CD8^+$ reactive cells was not sufficient to ameliorate the prostate cancer as the patients still had prostate cancer.

Applicants argue that a second concern raised in the action is the absence of clinical trials indicating any efficacy of a PSCA peptide vaccine. Thomas-Kaskel et al. have now reported the results of a clinical trial using PSCA14-22 and PSA peptide-loaded dendritic cells to vaccinate advanced prostate cancer patients (see. Thomas-Kaskel et al., Intl. J. Cancer 119:2428-2434 (2006), enclosed with IDS). The study concludes:

> The experience from this trial argues that DC-based vaccination against PSCA in the dose range given seems worthwhile for further clinical testing as a vaccination antigen. However, immunosuppression is likely to prevent higher rates of immune responders unless active immunotherapy is being employed earlier in the course of the disease, for example in the setting of a "PSA relapse" after radical prostatectomy. The correlation of immune responses with superior overall survival, further supported by documented regression of lymph node metastasis or impressive subjective pain relief, suggests that tumor-specific cellular immunity may indeed provide clinical benefit in CaP, although the optimal time point and vaccination schedule need further clarification.

These results demonstrate, contrary to the Action, that the *in vitro* observations as to the PSCA peptides *are predictable* in translating to the clinic.

Applicants arguments have been carefully considered, but have not been found persuasive because the teachings of Thomas-Kaskel et al. are not commensurate in scope with the claimed invention as none of the claims are drawn to using peptide-loaded dendritic cells to elicit an immune response and Thomas-Kaskel do not use any of the specifically claimed peptides. Although new claim 98 is drawn to the method of claim 53, wherein dendritic cells are used to present the claimed peptides to T cells in the context of MHC class I and II molecules, claim 98 depends on claim 53 where the PSCA proteins or fragments are administered to a subject directly, thus the claim does not read on administering peptide-loaded dendritic cells to a subject, but the mechanisms of presentation of the administered PSCA peptide.

Applicants argue that moreover, the very existence of such clinical trials strongly evidences that persons of ordinary skill in the art felt the art was reasonably predictable and ought to be so viewed by the Examiner. Indeed, the MPEP §2107.03 at 2100-35 right column provides:

> ... In order to determine a protocol for phase I testing, the first phase of clinical investigation, some credible rationale of how the drug might be effective or could be effective would be necessary. Thus, as a general rule, if an applicant has initiated human clinical trials for a therapeutic product or process, Office personnel should presume that the applicant has established that the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility.

Applicants arguments have been carefully considered, but have not been found persuasive because, as set forth above, the teachings of Thomas-Kaskel et al. are not commensurate in scope with the claimed invention as none of the claims are drawn to using

peptide-loaded dendritic cells to elicit an immune response and Thomas-Kaskel do not use any of the claimed peptides.

Applicants argue that thirdly, the Examiner cites Kiessling et al. as finding that only 2 of 8 tested peptide fragments bound to the HLA-A-201. Nothing in Kiessling indicates that it took undue experimentation to identify such peptide fragments. They used standard models to identify 8 candidates and found 2 fragments to be active (i.e., PSCA14-22 and PSCA~05_113). This hardly seems to involve undue amount of experimentation. The steps performed are routine and the amount of experimentation required to identify 2 useful agents, simply *minimal* for this field of art. The standard for enablement is not whether *any* experimentation is required but whether the amount of experimentation is undue. That some experimentation may be necessary to identify operative species does not constitute a lack of enablement. As the Federal Circuit has stated, "the key word is 'undue', not 'experimentation' " in determining whether pending claims are enabled. *Wands,* 8 U.S.P.Q.2d at 1405 (Fed. Cir. 1988). Indeed, a considerable amount of experimentation is permissible if it is merely routine, or if the specification in question provides a reasonable amount of guidance for practicing the invention.

Applicants arguments have been carefully considered, but have not been found persuasive because the teachings of Kiessling et al. are not commensurate in scope with the claimed because Kiessling et al. do not demonstrate that any immune response to any PSCA fragment is sufficient to treat any of the claimed cancers, as set forth above.

Applicants argue that without doubt, the pharmaceutical arts are one in which it is routine to screen a large number of agents in order to find useful ones. The expenditures of substantial

sums to practice an invention is no bar to enablement. Indeed, in the context of dose response, the Federal Circuit held in 1988 that if a specification teaches one embodiment and sets forth a method for determining dose/response, the experimentation required to determine a dose/response curve is not undue, even if the studies proved to cost approximately $50,000 and took 6-12 months to accomplish. *United States v. Telectronics,* 8 USPQ2d 1217 (Fed. Cir. 1988), *cert. denied,* 490 U.S. 1046 (1988).

Applicants arguments have been carefully considered, but have not been found persuasive because although one of ordinary skill could screen for the proteins that would function as claimed, in particular, screening assays do not enable the claimed invention because the court found in (*Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004) that screening assays are not sufficient to enable an invention because they are merely a wish or plan for obtaining the claimed chemical invention.

Applicants argue that previously, the Applicants cited Matsueda et al. as disclosing that one (i.e., PSCA76-84) of three tested peptides was active. Applicants now enclose with their IDS another Matsueda et al. reference which reports on the finding that two out of an additional 11 PSCA peptides (i.e., PSCA 7-15 and PSCA 21-30) were active (see, Matsueda et al., *Cancer Immunol. Immunother.* 53:479-489 (2004)). Having found them, Matsueda et al. again state that their peptides should be considered for use in clinical trials in immunotherapy. Clearly, persons of ordinary skill in the art are able to repeatedly identify suitable peptide fragments without much experimentation at all and these persons view the obtained peptides as being credible candidates for immunotherapy. The last sentence of Kiessling et al. is in accord on this last point:

Our results emphasize the suitability of PSCA target molecule for the immunotherapy of prostate cancer.

Applicants' arguments have been carefully considered, but have not been found persuasive because Matsueda et al. do not use any of the claimed peptides and, although Matsueda et al. showed that two peptides elicited an immune response, Matsueda et al. did not show that the immune response was effective to treat any tumor.

Applicants argue that the invention is in the field of polypeptide vaccine development. This field of art, drug development, is traditionally one in which a large volume of screening is both typical and routine. It is a field in which the courts have held that the necessary showing for enablement does not require testing in humans.

Applicants arguments have been carefully considered, but have not been found persuasive because although one of ordinary skill could screen for the proteins that would function as claimed, in particular, screening assays do not enable the claimed invention because the court found in (*Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004) that screening assays are not sufficient to enable an invention because they are merely a wish or plan for obtaining the claimed chemical invention. Although human testing is not required, neither the specification nor the art of record has provided data that is commensurate in scope with the claimed invention so as to enable the claimed invention.

Applicants argue that as set forth in previous papers, the specification provides all the guidance required to practice the invention. Without revisiting earlier remarks, the specification discloses the PSCA protein sequence, methods of identifying CTL and antibody epitope motifs

therein, and the importance of the elevation and specificity of PSCA expression in the subject cancers. Applicants argue that with respect to inducing an immune response as in claim 78, the specification also teaches all the steps necessary to induce an immune response against a PSCA protein or fragment thereof. However, the fact that the methods were not actually practiced in subjects with cancer is no bar to enablement (see, *Brana* decision). The use of a GST-PSCA polypeptide conjugate to induce a humoral response in mice without cancer is disclosed in Example 5 at page 89 of the original specification. The epitope domains of PSCA with respect to the various monoclonal antibodies is also disclosed in the paragraph bridging pages 92 and 93.

Applicants' arguments have been carefully considered, but have not been found persuasive because in the absence of a showing that the claimed methods will induce an immune response that will treat cancer the claims are not enabled for the reasons previously set forth.

Applicants argue that, as discussed above, the state of the art is high enough for others in the field to have already begun to practice the claimed invention largely as taught by the specification (see, above discussion of the Thomas-Kaskel et al., Matsueda et al., and Kiessling et al. art).

Applicants 'arguments have been carefully considered, but have not been found persuasive for the reasons set forth above and previously.

Applicants argue that with respect to antibodies against PSCA antigen in animals with PSCA expressing cancers, Zhang et al. have confirmed that vaccination with a DNA vaccine based on human PSCA and HSP70 adjuvant enhanced the antigen-specific CD8(+) T-cell

response and inhibited PSCA(+) Tumor growth in mice. (see, Zhang et al., *J Gene Med.* 9(8):715-26 (2007), enclosed with IDS).

Applicants' arguments have been carefully considered, but have not been found persuasive because the teachings of Zhang et al. are not commensurate in scope with the claimed invention as Zhang et al. is drawn to DNA vectors expressing PSCA and PSCA-HSP conjugates and are not treating with the proteins as claimed. Furthermore, it is noted Zhang et al. teaches that the PSCA alone vectors have little effect on tumor growth or survival of mice bearing PSCA expressing tumors, see figure 8, p. 723. Thus, assuming that the PSCA expressing from the DNA vector acts as a PSCA administered to a subject to elicit an immune response, as Applicants appear to be assuming, Zhang et al. demonstrates that PSCA alone is ineffective for cancer treatment.

Applicants argue that no art is without its uncertainty. However, the results achieved by Thomas-Kaskel et al., Matsueda et al., Kiessling et al., and Zhang et al. show that the uncertainties posed by the Examiner were no bar to others' practice of the Applicants' methods. In particular, as discussed above, the existence of clinical studies in and of itself is strong evidence that persons in the field consider the uncertainty in the art to be acceptably low. Applicants argue that the quantity of experimentation necessary to practice the invention with exemplified and non-exemplified aspects appears to be well within what is routinely performed by a person of ordinary skill in the art of therapeutics development. Applicants argue that as set forth in the MPEP §2164.01 (a), the final step in making the determination that "undue experimentation" would have been needed to make and use the

claimed invention is reached by weighing all the above noted factual considerations. *In re Wands,* 858 F.2d at 737, 8 USPQ2d at 737." Considering all the above, the simple fact is *that persons in the art are using the claimed invention successfully with no sign of undue experimentation.*

Applicants' arguments have been carefully considered, but have not been found persuasive because Applicants are reiterating arguments set forth above, thus for the reasons set forth above and previously undue experimentation would be required to practice the claimed methods.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

6. If Applicants were able to overcome the rejections set forth above, claims 53, 58-64, 67, 70, 71, 74, 77-88, 91, 93-100 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for A method for inducing a cellular immune response in a human or mammalian subject directed to a PSCA protein of Fig. 1B SEQ ID NO:2, the subject having a cancer overexpressing a **PSCA protein of Fig. 1B (SEQ ID NO:2)**, said cancer selected from the group consisting of prostate cancer, prostate cancer metastasized to bone, bladder cancer, and pancreatic cancer, the method comprising administering to the subject a PSCA protein of Fig. 1B (SEQ ID NO:2) or an immunogenic fragment thereof, *does not* reasonably provide enablement for a method for inducing a cellular immune response in a human or mammalian subject directed to a PSCA protein of Fig. 1B SEQ ID NO:2, the subject having a cancer overexpressing **a Prostate Stem Cell Antigen (PSCA)** protein, said cancer selected from the group consisting of prostate cancer, prostate cancer metastasized to bone, bladder cancer, and

pancreatic cancer, the method comprising administering to the subject a PSCA protein of Fig. 1B (SEQ ID NO:2) or an immunogenic fragment thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to a method for inducing a cellular immune response in a human or mammalian subject directed to a PSCA protein of Fig. 1B SEQ ID NO:2, the subject having a cancer overexpressing a Prostate Stem Cell Antigen (PSCA) protein, said cancer selected from the group consisting of prostate cancer, prostate cancer metastasized to bone, bladder cancer, and pancreatic cancer, the method comprising administering to the subject a PSCA protein of Fig. 1B (SEQ ID NO:2) or an immunogenic fragment thereof.

The specification teaches that one aspect of the invention provides various PSCA proteins and peptide fragments thereof as used herein, PSCA refers to a protein that has the amino acid sequence of human PSCA as provided in FIGS. 1B and 3, the amino acid sequence of the murine

PSCA homologue as provided in FIG. 3, or the amino acid sequence of other mammalian PSCA homologues, as well as allelic variants and conservative substitution mutants of these proteins that have PSCA activity. The PSCA proteins of the invention include the specifically identified and characterized variants herein described, as well as allelic variants, conservative substitution variants and homologs, see para 0095 of the published application.

The specification teaches that the term "PSCA" includes all naturally occurring allelic variants, isoforms, and precursors of human PSCA as provided in FIGS. 1B and 3 and murine PSCA as provided in FIG. 3. In general, for example, naturally occurring allelic variants of human PSCA will share significant homology (e.g., 70-90%) to the PSCA amino acid sequence provided in FIGS. 1B and 3. Allelic variants, though possessing a slightly different amino acid sequence, may be expressed on the surface of prostate cells as a GPI linked protein or may be secreted or shed. Typically, allelic variants of the PSCA protein will contain conservative amino acid substitutions from the PSCA sequence herein described or will contain a substitution of an amino acid from a corresponding position in a PSCA homologue such as, for example, the murine PSCA homologue described herein, see para 0096 of the published application.

The specification teaches that one class of PSCA allelic variants will be proteins that share a high degree of homology with at least a small region of the PSCA amino acid sequences presented in FIGS. 1B and 3, but will further contain a radical departure from the sequence, such as a non-conservative substitution, truncation, insertion or frame shift. Such alleles are termed mutant alleles of PSCA and represent proteins that typically do not perform the same biological functions, see para 0097 of the published application.

One cannot extrapolate the teachings of the specification to enable the scope of the claims because no nexus has been established between the broadly contemplated PSCA protein and its expression in the claimed cancers because 1) it is well known in the art that the expression pattern of one protein variant does not predict the expression pattern of other related variants. Additionally, even if the claimed variants were expressed in the claimed cancers, 2) it could not be predicted that treatment with SEQ ID NO: 2 or an immunogenic fragment thereof would elicit an immune response that would be specific for all of the variants of PSCA contemplated as immune responses require specific recognition of the antigen through protein binding interactions (antibody or T-cell receptor) and the exquisite sensitivity of antigen-antibody interactions to even single amino acid sequence changes is well known in the art.

1) As drawn to the expression of protein variants, it is well known in the art that that the expression pattern of one protein variant cannot be predictably extrapolated to that of another variant. In particular, there are many examples known in the art of differing expression patterns of protein variants such as those produced by splice variants. Jiang et al (JBC, 2003, 278(7) 4763-4769) specifically teach that the type 3 Ca2+ release channel protein, RyR3, exhibits seven tissue specific alternatively spliced variants of RyR3. The authors conclude that tissue-specific expression of RyR3 splice variants is likely to account for some of the pharmacologic and functional heterogeneities of RyR3 (see abstract). The abstract of Matsushita et al (FEBS Letters, 1999, Vol. 443, pp. 348-352) teaches that latrophilins exhibit alternative splicing resulting in latrophilin-1, which is present in brain and endocrine cells, latrophilin-2, which is ubiquitous, and latrophilin-3 which is brain-specific. The abstract of Singh et al (Glycobiology, 2001, Vol. 11, pp. 587-592) teach that

the CD44 splice variant, CD44v, is the major PNA-binding glycoprotein in colon cancer cells in contrast to standard CD44. These references serve to demonstrate that one of skill in the art cannot anticipate the tissue distribution of one protein variant, such as splice variants, based on the tissue distribution of the wild-type protein or a single protein isoform.

Thus, it is clear that one could not reliably predict which of the broadly claimed PSCA proteins would be involved in the etiology or pathology of prostate, bladder, or pancreatic cancer or which would be an appropriate target so that the method would function as claimed. The specification provides neither information nor guidance on how to predictably identify which of the broadly claimed PSCA will be expressed in prostate, bladder, or pancreatic cancer. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention would function as broadly claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention. Thus, undue experimentation would be required to make and use the invention as broadly claimed

2) As drawn to the sensitivity of binding proteins to even minor changes in amino acid sequences, Rudikoff et al (Proc. Natl. Acad. Sci. USA 1982 Vol. 79 pages 1979 -1983) teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. Additionally, Coleman et al. (Research in Immunology, 1994; 145(1): 33-36) teach single amino acid changes in an antigen can effectively abolish antibody antigen binding. Furthermore, Abaza et al. (Journal of Protein Chemistry,

Vol. 11, No. 5, 1992, pages 433-444) teach single amino acid substitutions outside the antigenic site on a protein affects antibody binding. Further, the sensitivity of binding proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. These references demonstrate that even a single amino acid alteration or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristics of a binding protein. Given the above, it is not possible to predict whether the generation of an immune response to SEQ ID NO: 2 or immunogenic fragments thereof would predictably be able to affect a cancer cell expressing the broadly claimed variants because both cellular and humoral mediated immune responses depend on the ability of proteins (T cell receptors or antibodies) to recognize their target through specific protein to protein interactions. Thus one cannot predict that the invention will function as claimed with a reasonable expectation of success. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention would function as claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to use the claimed invention.

7. Claims 53, 58-64, 67, 70, 71, 74, 77-88, 91, 93-100 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are broadly drawn to a method for inducing a cellular immune response in a human or mammalian subject directed to a PSCA protein of Fig. 1B SEQ ID NO:2, the subject having a cancer overexpressing a Prostate Stem Cell Antigen (PSCA) protein, said cancer selected from the group consisting of prostate cancer, prostate cancer metastasized to bone, bladder cancer, and pancreatic cancer, the method comprising administering to the subject a PSCA protein of Fig. 1B (SEQ ID NO:2) or an immunogenic fragment thereof.

The state of the art is such that it is well known in the art that expression pattern of one protein variant does not predictably extrapolate to the expression pattern of other related variants. In particular, there are many examples known in the art of differing expression of protein variants, such as those produced by splice variants. Jiang et al (JBC, 2003, 278(7) 4763-4769) specifically teach that the type 3 Ca2+ release channel protein, RyR3, exhibits seven tissue specific alternatively spliced variants of RyR3. The authors conclude that tissue-specific expression of RyR3 splice variants is likely to account for some of the pharmacologic and functional heterogeneities of RyR3 (see abstract). The abstract of Matsushita et al (FEBS Letters, 1999, Vol. 443, pp. 348-352) teaches that latrophilins exhibit alternative splicing resulting in latrophilin-1, which is present in brain and endocrine cells, latrophilin-2, which is ubiquitous, and latrophilin-3 which is brain-specific. The abstract of Singh et al (Glycobiology, 2001, Vol. 11, pp. 587-592) teach that the CD44 splice variant, CD44v, is the major PNA-binding glycoprotein in colon cancer

cells in contrast to standard CD44. These references serve to demonstrate that one of skill in the art cannot anticipate the tissue distribution of protein variant, such as splice variants, based on the tissue distribution of the wild-type protein or a single protein isoform.

Additionally, the specification teaches that one aspect of the invention provides various PSCA proteins and peptide fragments thereof as used herein, PSCA refers to a protein that has the amino acid sequence of human PSCA as provided in FIGS. 1B and 3, the amino acid sequence of the murine PSCA homologue as provided in FIG. 3, or the amino acid sequence of other mammalian PSCA homologues, as well as allelic variants and conservative substitution mutants of these proteins that have PSCA activity. The PSCA proteins of the invention include the specifically identified and characterized variants herein described, as well as allelic variants, conservative substitution variants and homologs, see para 0095.

The specification teaches that the term "PSCA" includes all naturally occurring allelic variants, isoforms, and precursors of human PSCA as provided in FIGS. 1B and 3 and murine PSCA as provided in FIG. 3. In general, for example, naturally occurring allelic variants of human PSCA will share significant homology (e.g., 70-90%) to the PSCA amino acid sequence provided in FIGS. 1B and 3. Allelic variants, though possessing a slightly different amino acid sequence, may be expressed on the surface of prostate cells as a GPI linked protein or may be secreted or shed. Typically, allelic variants of the PSCA protein will contain conservative amino acid substitutions from the PSCA sequence herein described or will contain a substitution of an amino acid from a corresponding position in a PSCA homologue such as, for example, the murine PSCA homologue described herein, see para 0096 of the published application.

Given the above, it is clear that an adequate written description is essential for one of skill in the art to make and use the claimed invention using the broadly claimed cancer cells expressing a PSCA.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of a cancer overexpressing a PSCA protein, per Lilly by structurally describing a representative number of PSCA proteins expressed by cancer or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe a cancer overexpressing a PSCA protein, nor does the specification provide any partial structure of a PSCA protein overexpressed in cancer, nor any physical or chemical characteristics of a PSCA protein overexpressed in cancer nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses SEQ ID NO: 2 overexpression in cancer, this does not provide a description of a cancer overexpressing a PSCA protein.

The specification also fails to describe a cancer overexpressing a PSCA protein by the test set out in Lilly. The specification describes only SEQ ID NO: 2 overexpression in cancer. Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of a cancer overexpressing a PSCA protein that is required to practice the claimed invention or reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the broadly claimed invention. Since the specification fails to adequately describe or reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the broadly claimed invention that is the broadly claimed cancer overexpressing a PSCA protein, it also fails to adequately describe the claimed

method or reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

8. Claims 67 and 91 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of the PSCA protein fragment consists of amino acids 21 through 99 as described in SEQ ID NO: 2 has no support in the specification and the claims as originally filed. Although claim 67 was filed as a preliminary amendment on May 14, 2001, preliminary amendments presented on the filing date are not part of the original disclosure unless referred to in the first executed oat or declaration in applications filed before September 21, 2004. Applicants point to support for claim 67 and 91, in the originally-filed specification at page 6, lines 18-23; and Figure 3; and page 92, lines 6-7. A review of the specification discloses support for an alignment of PSCA from mouse and human and hSCA-2 (page 6, lines 18-23; and Figure 3) and a monoclonal antibody against PSCA lacking its signal sequences (page 92, lines 6-7). The suggested support is not found persuasive because there is nothing in the specification to suggest a PSCA protein fragment consisting of amino acids 21 through 99 of SEQ ID NO: 2. The subject matter claimed in claims 67 and 91 broadens the scope of the invention as originally disclosed in the specification. Applicants can cancel the claimed subject matter or submit a supplemental oath or declaration under 37 CFR 1.67 referring to both the application and the preliminary amendment filed with the original application to obviate this rejection, see MPEP 60804(b).

9. No claims allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Helms Larry can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Susan Ungar

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

/Peter J. Reddig/
Examiner
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PJR